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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/152,698	09/02/1998	REGUPATHY MADIYALAKAN	A52023.1	4505

28120 7590 04/29/2004

ROPES & GRAY LLP
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BOSTON, MA 02110-2624

EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/152,698

Applicant(s)

MADIYALAKAN ET AL.

Examiner

Karen A Canella

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 30,71,73-76,85-89,91-96 and 98-115 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 30,71,73-76,85-89,91-96 and 98-115 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |



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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER
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20040426

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

1. In response to applicant's inquiry regarding the last Office action, the following corrective action is taken.
2. The period for reply of 3 MONTHS set in said Office Action is restarted to begin with the mailing date of this letter.
3. A complete copy of the last Office Action is enclosed.

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER

Karen A. Canella, Ph.D.
Art Unit 1642
April 26, 2004

DETAILED ACTION

Claims 30, 71, 73, 74, 85-89, 91, 92, and 94 have been amended. claims 99-115 have been added. Claims 30, 71, 73-76, 85-89, 91-96, 98-115 are pending and under consideration.

It is noted that all claims are not drawn to tumor antigens, thus the priority filing date of May 15, 1996 is reinstated.

Claim 94 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how claim 94 further limits claim 85. Claim 85 recites a composition comprising a soluble complex of a tumor associated antibody and an antibody or antigen binding fragment thereof, wherein administration of the composition to a host results in a multi-epitopic immune response. Claim 94 recites the limitation of a "multi-epitopic tumor associated antigen". The tumor associated antigen of claim 85 would inherently be multi-epitopic in order to produce a multi-epitopic immune response as required in claim 85. thus it is unclear how claim 94 further limits the scope of claim 85.

Claims 30, 71, 73-76, 85-89, 91-96, 98-115 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 30 and 85 have been amended to recite "soluble complex formed from a tumor associated antigen and an antibody or antigen binding fragment thereof". New claims 103-110 also incorporate this term. the specification states on page 14 that the binding agent alone, the binding agent-soluble antigen complex, either acting as an immunogen, alters the immunogenic condition of the host". This is insufficient support for the term "soluble complexes" because the specification described only an antibody complex with a soluble antigen rather than a soluble antigen-antibody complex as now claimed.

Claims 30, 71, 73-76, 85-87, 91-96, 98, 101, 103-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al ('Cancer Immunotherapy' In: Advances in Cancer Research, 1992, vol. 59, pp. 245-323) in view of Crowley et al (Journal of Experimental Medicine, 1990, vol. 172, pp. 383-386) and Steinman et al (WO 93/20185) and Sallusto et al (Journal of Experimental Medicine, 1994, vol. 179, pp. 1109-1118) and de La Salle et al ('FcγR on Human Dendritic Cells' In: Human IgG Receptors, 1996, pp. 39-55, Van de Winkel et al Eds), and Schwartz ('Cancer Markers' In: Cancer: Principles and Practice of Oncology, 4th Edition, vol. 1, 1994, DeVita et al, Ed.s., page 531-542, cited in a previous Office action).

Claim 30 is drawn to a method of stimulating a multi-epitopic immune response to a tumor associated antigen comprising administering to a host a soluble complex formed from a tumor-associated antigen and an antibody or antigen binding fragment thereof that binds to a first epitope of the tumor-associated antigen wherein the soluble complexes induces host antibodies reactive with at least one other epitope of the antigen. Claim 71 embodies the method of claim 30, wherein the antibody is selected from the group consisting of a monoclonal antibody, a single chain antibody, a humanized antibody and a chimera antibody. Claim 73 embodies the method of claim 30 wherein the antigen is associated with a human disease or condition. Claim 74 embodies the method of claim 73 wherein the human disease or condition is selected from the group consisting of cancer and tumor. Claim 75 embodies the method of claim 74 wherein the cancer is selected from the group consisting of breast, ovarian, prostate and gastro-intestinal cancers. Claim 76 embodies the method of claim 30 wherein the host is human. Claim 98 embodies the method of claim 30 wherein the antibody is a non-human antibody. Claim 101 embodies the method of claim 30, wherein tumor-associated antigen is an ovarian tumor-associated antigen. Claim 102 embodies the method of claim 101, wherein the ovarian tumor-associated antigen is CA125. Claim 103 embodies the method of claim 30, wherein the soluble complex induces cytotoxic T cells reactive with at least one other epitope of the antigen.

Claim 85 is drawn to a composition for altering immunogenicity of a tumor-associated antigen comprising a soluble complex of tumor associated antigen and an antibody or antigen-binding fragment thereof that specifically binds an epitope of the antigen, wherein administration of the composition to a host results in a multi-epitopic immune response including

production of antibodies reactive with at least one other epitope associated with the antigen. Claim 86 embodies the composition of claim 85 wherein the antibody is selected from the group consisting of a monoclonal antibody, a single chain antibody, a humanized antibody and a chimera antibody. Claim 87 embodies the composition of claim 85 wherein the antibody is a monoclonal antibody. Claim 91 embodies the composition of claim 85 wherein the antigen is associated with a human disease or condition. Claim 92 embodies the composition of claim 91 wherein the human disease or conditions is selected from the group consisting of cancer and tumor. Claim 93 embodies the composition of claim 92 wherein the cancer is selected from the group consisting of breast, ovarian, prostate, and gastro-intestinal cancers. Claim 94 embodies the compositions of claim 85 wherein the antigen is a multi-epitopic tumor associated antigen. Claim 95 embodies the composition of claim 85 wherein the antigen is a shed soluble antigen. Claim 96 embodies the compositions of claim 85 wherein the host is a human. Claim 114 embodies the composition of claim 85, wherein the antibody is a non-human antibody. Claim 115 embodies the composition of claim 85, wherein the antigen is a circulating soluble antigen.

Claim 104 is drawn to a method of stimulating a multi-epitopic immune response to a tumor-associated antigen comprising administering to a host a soluble complex formed from an antigen and an antibody or antigen binding fragment thereof that binds to a first epitope of the tumor-associated antigen, wherein the soluble complex induces host antibodies and cytotoxic T cells reactive with at least one other epitope of the antigen.

Claim 105 is drawn to a method of stimulating a multi-epitopic immune response to a tumor-associated antigen comprising administering to a host a soluble complex formed from an antigen and an antibody or antigen binding fragment thereof that binds to a first epitope of the tumor-associated antigen, wherein the soluble complex induces cytotoxic T cells reactive with at least one other epitope of the antigen. Claim 106 embodies the method of claim 105, wherein the soluble complex further induces host antibodies reactive with other epitopes of the antigen.

Claim 107 is drawn to a method of treating an oncological disease comprising administering to a host a soluble complex formed from a tumor-associated antigen and an antibody or antigen binding fragment thereof that binds to a first epitope of the tumor-associated antigen, wherein the soluble complex induces host antibodies reactive with at least one other epitope of the antigen. Claim 108 embodies the method of claim 107, wherein the soluble

complex induces cytotoxic T cells reactive with other epitopes of the antigen. Claim 110 embodies the method of claim 107, wherein the soluble complex induces host antibodies reactive with other epitopes of the antigen.

Claim 109 is drawn to a method of treating an oncological disease comprising administering to a host a soluble complex formed from a tumor-associated antigen and an antibody or antigen binding fragment thereof that binds to a first epitope of the tumor-associated antigen, wherein the soluble complex induces cytotoxic T cells reactive with at least one other epitope of the antigen.

Claim 113 embodies the method of any of claims 30, 104, 105, 107, and 109, wherein the antibody is anon-human antibody.

Kedar et al teach that tumor cell populations are heterogeneous comprising c4lls with variable sensitivities to immunological effector mechanisms. Kedar et al teach that tumor samples collected from a individual often react differently with antibodies and CTL clones. Kedar et al teach that "cocktails" of different antibodies and/or several T-cell clones directed against different antigenic epitopes of the tumor may be required for control of the tumor. (page 255, section C under the heading of "Heterogeneity of the Tumor Cell Population").

Crowley et al teach that peptide fragments of proteins are endocytosed by antigen-presenting cells and then bound to MNC products on the surface of said antigen-presenting cells (page 383, first column, lines 1-5). Crowley et al teach that when antigens are administered to animals and the dendritic cells of said animals are isolated, said dendritic cells are carrying the antigen in an immunogenic form (page 383, first column, lines 7-9). Crowley et al teach that when myoglobin was administered to mice, the dendritic cells taken from said mice were able to activate three different T-cell clones (Table 1: H-2d + myoglobin).

Steinman et al teach that dendritic cells are termed "nature's adjuvant" because aid cells are capable of directly priming T cells that recognize only antigens presented by the particular MHC class of the presenting dendritic cell and because dendritic cells are capable of capturing antigens in an immunogenic form in situ (page 33, lines 16-23). Steinman et al include tumor antigens as the antigens presented by dendritic cells (page 33, lines 14-16). Steinman et al teach that dendritic cells are capable of processing complex antigens into those peptides that would be presented by self MHC products (page 33, lines 29-31).

Sallusto et al teach that the efficiency of soluble antigen presentation by dendritic cells can be enhanced by specific antibodies via Fc Receptor-mediated antigen uptake (title and abstract, lines 8-10). Sallusto et al teach that dendritic cells have pinocytic activity and that the Fc receptor II on dendritic cells can be used to increase the uptake of antigen in antigen-antibody complexes (page 1110, first column, lines 11-13) which results in antigen-presentation and stimulation of naive T-cells (page 1110, first column, lines 5-6 and lines 13-16). Sallusto et al teach that dendritic cells were the most effective of the antigen-presenting cells at presenting a soluble antigen and that in the presence of the antibody that binds to said antigen presentation increased 100-fold (page 1111-1112, under the heading "Efficient presentation of soluble Antigen and Antibody-antigen complexes by Immature Dendritic Cells" and page 1115, second column, lines 16-20).

De la Salle et al teach that presentation of exogenous soluble antigens to helper T-cells is a complex process which requires uptake of proteins by antigen presenting cells, digestion of said proteins into immunogenic peptides, the intracellular association of the immunogenic peptides with MHC II molecules and the transport of the resulting immunogenic complexes to the plasma membrane for recognition by antigen specific T-cells (page 46, lines 20-26). De la Salle et al teach that targeting of antigens to Fcγ Receptor on Langerhans cells by means of immune complexes comprising IgG complexed to its target soluble antigen resulted in antigen presentation at dramatically reduced levels of soluble antigen and that this process required both the uptake of immune complexes via the Fcγ receptor and the processing of the antibody-complexed soluble antigen by the Langerhan's cells (page 46, lines 37-45).

Schwartz teaches tumor markers that are shed into the serum of cancer patients having breast, ovarian, prostate and gastro-intestinal cancers (Table 21-5). These markers include PSA.

It would have been prima facie obvious at the time the invention was made to stimulate an immune response against more than one epitope of a tumor associated antigen by administering to a patient having a tumor a soluble complex of a tumor -associated antigen complexed to an antibody or antigen binding fragment thereof comprising an Fc region. One of skill in the art would have been motivated to do so by the teachings of

1. Kedar et al on the desirability of having several T-cell clones directed against different antigenic epitopes of the tumor may be required for control of the tumor;

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2. Crowley et al on the ability of dendritic cells exposed in vivo to exogenous antigen to present multiple immunogenic epitopes to T-cells;
3. Steinman et al on the capability of dendritic cells to processing complex antigens into those peptides that would be presented by self MHC products;
4. Sallusto et al on the enhancement of soluble antigen presentation by dendritic cells through the uptake of antigen-antibody complexes;
5. De La Salle et al on the enhancement of soluble antigen presentation by Langerhan's cells by antigen-antibody complexes and the required processing of the antigen within the antigen-antibody complex after uptake via the Fc receptor of the dendritic cell;
6. Schwartz on tumor antigens which are shed from breast, ovarian, prostate and gastrointestinal tumors and present as soluble antigens in the serum of cancer patients.

One of skill in the art would recognize after reading of the above prior art references, that dendritic cells are capable of taking up soluble antigen in the form of antigen-antibody complexes in a process that involves internalization from the Fc receptor which is separate from the process of uptaking particulate antigens, and that antigens which are internalized by dendritic cells are processed into immunogenic fragments which are presented on the surface of said dendritic cell. One of skill in the art would also recognize that if a complex exogenous antigen were internalized by a dendritic cell more than one immunogenic epitope can be presented to a T-cell, such as was illustrated in the teachings of Crowley et al. One of skill in the art would be motivated to provide more than one immunogenic epitope of a tumor associated antigen in order to activate more than one T-cell against said antigen after reading the teachings of Kadar et al on the desirability of having several T-cell clones and antibodies directed against different antigenic epitopes of the tumor in order to circumvent the problem of antigenic heterogeneity exhibited by a tumor mass.

Claims 30, 71, 73-76, 85-87, 91-96, 98, 101, 103-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz as applied to claims 30, 71, 73-76, 85-87, 91-96, 98, 101, 103-110 and 113-115 above, and further in view of Schlom ('Monoclonal

Antibodies: they're more and less than you think', In: Molecular Foundations of Oncology, 1991, pp. 95-133, cited in a previous Office action).

The specific embodiments of claims 30, 71, 73-76, 85-87, 91-96, 98, 101, 103-110 and 113-115 are set forth above. the combination of prior art references renders obvious methods of treating oncological disease and methods of stimulating a multi-epitopic response to a tumor associated antigen comprising the administration of a soluble complex comprising a tumor associated antigen and a monoclonal antibody having a Fc region for the reasons set forth above. Claims 71 and 86 are further drawn to a single-chain antibody, a humanized antibody and a chimeric antibody.

The combination of the references does not specifically address humanized or chimerized antibodies in the soluble complex.

Schlom teaches that HAMA response develop in more than 90% of patients receiving more than three doses of a monoclonal murine Antibody and that it is unrealistic to assume that one or two doses or a given anti-cancer therapeutic would be effective. Schlom concludes that because of the HAM response only the first and perhaps the second administration of the antibody actually reached the tumor site in a therapeutically effective amount. Schlom teaches the use of recombinant chimeric antibodies contain a human Fc region to avoid the HAMA response (page 98 second column, second full paragraph to page 99, first column, first paragraph).

It would have been prima facie obvious at the time the invention was made to use humanized or chimeric antibodies comprising a human Fc region for the administration to humans of the soluble complexes rendered obvious by the combination of Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz. One of skill in the art would be motivated to do so by the teachings of Schlom on the necessity of avoiding the HAMA response in patients undergoing immunotherapy for cancer, and the teachings of Schlom on the avoidance of the HAMA response by the administration of antibodies having a human Fc domain.

Claims 30, 71, 73-76, 85-87, 91-96, 98, 99, 101, 103-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and

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Sallusto et al and De La Salle et al and Schwartz as applied to claims 30, 71, 73-76, 85-87, 91-96, 98, 101, 103-110 and 113-115 above, and further in view of Dong et al (In: Vaccine Design: The Subunit Approach, Powell et al, Ed., 1995, pp. 625-643).

Claim 99 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is administered with an adjuvant.

The combination of Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz does not specifically teach the administration of a cytokine as an adjuvant.

Dong et al teach cytokines as vaccine adjuvants. Dong et al teach that cytokines both increase the number of antigen-presenting cells that can present antigens, and activate said antigen presenting cells (page 626, last sentence).

It would have been prima facie obvious at the time the claimed invention was made to administer the soluble complex with a cytokine as an adjuvant. One of skill in the art would be motivated to do so by the teachings of Dong et al on the use of cytokines as adjuvants to stimulate antigen presentation and activate antigen presenting cells.

Claims 30, 71, 73-76, 85-88, 91-96, 98, 101-110 and 113-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz as applied to claims 30, 71, 73-76, 85-87, 91-96, 98, 101, 103-110 and 113-115 above, and further in view of O'Brien (US 5,976,818) and Baum et al (Cancer Research, 1994, vol. 73, 3 suppl., pp. 1121-1125, cited in the previous Office action).

Claim 88 embodies the composition of claim 87 wherein the monoclonal antibody is produced by the hybridoma having the ATCC deposit number PTA-1883. the specification identifies said deposited hybridoma as producing the B43.13 antibody. Claim 102 embodies the method of claim 101 wherein the ovarian associated antigen is CA125.

O'Brien teaches that CA125 is an ovarian tumor antigen in the extracellular matrix of CA-125 .
producing cells (abstract) , ascites fluid and tumor serum (column 4, line 3). It can be concluded that CA 125 is a shed tumor antigen.

Baum et al teach that the B43.13 antibody binds to CA-125 of ovarian cancer cells (page 1122, first column, under the heading "Monoclonal Antibodies").

It would have been prima facie obvious to one of skill in the art at the time the invention was made to use a complex of B43.13 bound to CA-125 to alter the immunogenicity of Ca-125 and treat ovarian cancer. One of skill in the art would have been motivated to do so by the teachings of O'Brien on CA-125 as a tumor antigen found in the serum and ascites of patients having an ovarian tumor. One of skill in the art would have concluded that CA-125 is a shed antigen and is soluble in the serum and ascites, and is therefore present as a circulating tumor antigen. One of skill in the art would also conclude that the B43.13 antibody bound an epitope of CA-125 that was antigenically exposed on the tumor antigen and therefore a complex between B43.13 and shed CA-125 could be formed.

Claims 30, 71, 73-76, 85-87, 91-96, 98, 100, 101, 103-111 and 112-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al and Crowley et al and Steinman et al and Sallusto et al and De La Salle et al and Schwartz as applied to claims 30, 71, 73-76, 85-87, 91-96, 98, 101, 103-110 and 113-115.

Claim 100 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is formulated at dose of from about 0.1 ug to about 2 mg per kilogram of body weight of the host. Claim 111 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is formulated at dose of about 2 mg per host. Claim 112 embodies the method of claim 30 wherein the antibody or antigen-binding fragment thereof is formulated at dose of about 0.1 ug to about 200 ug per kilogram of body weight of the host.

None of the aforesaid prior art references teaches or suggests the specific dosages claimed. however, it is recognized in the art that the establishment of optimal dosages is empirical but within the purview of one of skill in the art.

It would have been prima facie obvious to optimize the dosage of antigen-antibody complexes used in the claimed methods to the recited values and ranges. One of skill in the art would have been motivated to do so in order to most effectively treat individuals having tumors.

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The provisional rejection of claims 30, 71, 73-76, 85-88 and 91-97 under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 10 and 14-37 of co-pending application 09/641,833 in view of Madiyalakan et al and Klaus et al and the abstract of Bachmann et al is withdrawn in light of the cancellation and amendment of the '833 claims.

All other rejections and objections as stated in the previous Office action are withdrawn in light of applicants amendments.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

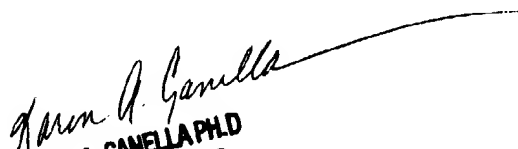
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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

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04/05/04


KAREN A. CANELLA PH.D.
PRIMARY EXAMINER